

Appl. No.: 10/762,078
Amdt. dated 10/11/2007
Reply to Office action of May 11, 2007

REMARKS/ARGUMENTS

Claims 1-4, 8-15, and 17-31 are currently pending in the subject application. Claims 1-4, 8-15, and 17-31 presently stand rejected. Claims 9-10, 22-28, and 31 have been amended by the present amendment. Claims 1-4, 8-15, 17-21, and 29-30 have been canceled by the present Amendment. New claims 32-33 have been added by the present amendment. Therefore, upon entry of the present amendment, claims 9-10, 22-28, and 31-33 will remain pending in the subject application. A substitute specification is enclosed herewith. No new matter is added by way of claim amendment. Reexamination and reconsideration of the claims are respectfully requested in view of these amendments and the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejection of Claims 1-31 Under 35 U.S.C. § 112, First Paragraph

Should Be Withdrawn

Claims 1-31 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action acknowledges that the specification is enabled for a limited number of nucleotides linked through a terminal phosphate group to a solid support and the synthesis thereof. The Office Action asserts, however, that the specification does not reasonably provide enablement for the vast array of compounds, some linked to a solid support and some not linked to a solid support, and the synthesis thereof, encompassed by instant claims 1-30, and to the method of testing encompassed by claim 31. Applicants note that claims 5-7, and 16 were canceled in the Amendment dated January 26, 2007, thereby rendering moot this rejection with respect to claims 5-7, and 16.

More particularly, the Office Action asserts that “[t]he fundamental issue ... is whether practicing the full scope of the instant invention is possible without undue experimentation.” Office Action at page 2. The Office Action then recites the factors related to “undue experimentation” enumerated in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q. 2d, 1400, 1404 (Fed. Cir. 1988).

A. The breath of the claims: The Office Action asserts that the reliance of the independent claims on incompletely defined or non-defined terminology renders the claim[s]

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vastly over broad in scope. As provided in more detail herein below, Applicants have canceled independent claim 1, added new independent claim 32, and have amended independent claims 28 and 31 to more completely define the terminology recited therein.

B. The nature of the invention: The Office Action asserts that the invention is directed to compounds wherein a terminal 5'-nucleotidyl unit with optionally multiple O-P-O linkages is attached to an intermediate linker or linkers and these linkers are ultimately alternatively attached to a solid support, "a tag," or "a protective group." Without acquiescing to the Office Action's characterization of the presently disclosed subject matter, Applicants note that claims 1, 28, and 31 were amended in the Amendment dated January 26, 2007, by deleting therefrom the terms "tag" and/or "protective group." At that time, Applicants also canceled claim 16, which depends from claim 1 and further defined the term "tag." Accordingly, Applicants respectfully submit that the claims as currently amended are directed to embodiments of compositions of Formula I wherein the variable "Y" is "a solid support." Applicants further submit that embodiments of Formula I wherein Y is a solid support and their synthesis are enabled by the numerous examples and figures disclosed in the application as filed.

C. The state of the prior art: Applicants note that the Office Action acknowledges that there is no single reference that discloses all of the details of the claimed compounds, their method of making, or their application in affinity chromatography.

D. The level of one of ordinary skill: The Office Action acknowledges that one of ordinary skill would not find the syntheses or the affinity chromatography methods disclosed in the subject application to be difficult to execute if the compounds being used therefor are defined as provided for in the numerous examples found in the disclosure. As provided in more detail herein below, Applicants respectfully submit that the compounds in the claims as currently amended enable one of ordinary skill to make and use the claimed compounds.

E. The level of predictability in the art: The Office Action acknowledges that compounds having structures similar to the prior art affinity chromatography supports are likely to provide results similar to those established by the prior art, but asserts that this conclusion does not necessarily apply to all of the compounds encompassed by the claims.

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F. The amount of direction provided by the inventor: The Office Action acknowledges that the instant disclosure provides a large number of examples of how to make compounds usable in affinity chromatography, but only one prospective description describing how these compounds might be applied to actual affinity chromatographies.

G. The existence of working examples: The Office Action asserts that there are many synthetic working examples, but no working examples of how any one of the instant disclosed compounds may be used to carry out affinity chromatography. The Office Action also asserts that there are no working examples wherein the nucleotidyl moiety is attached to a protecting group or to a "tag." As noted hereinabove, claims 1, 28, and 31 were amended in the Amendment dated January 26, 2007, by deleting therefrom the term "tag" and by canceling claim 16, which depends from claim 1 and further defined the term "tag." Therefore, Applicants respectfully submit that the amendments of January 26, 2007, render moot this comment in relation to the term "tag."

H. In sum, the Office Action asserts that the quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be undue because the scope of the claims allegedly is excessive and because of the total absence of working examples to provide guidance concerning whether the instant compounds actually behave in a predictable manner based on the prior art experience of others with similar affinity chromatographic-capable compounds.

In response to paragraphs F, G, and H summarized immediately hereinabove, Applicants note that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Manual of Patent Examining Procedure (hereinafter "MPEP") § 2164.01 (quoting *United States v. Teletronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988) (emphasis added). Applicants respectfully submit that the use of γ -phosphate-linked ATP affinity columns for purifying, for example, a protein kinase, see, e.g., U.S. Patent No. 5,536,822 to Haystead (hereinafter "the '822 patent"), and for screening diverse arrays of materials for bioactive compounds, see, e.g., PCT International Patent Application Publication No. WO 00/63694 to Haystead, each of which is incorporated by reference in the

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subject application, is known in the art. Accordingly, one of ordinary skill in the art upon review of the instant disclosure and what is known in the art could use the presently disclosed nucleotide affinity medium of Formula I for screening a test compound as recited in claim 31 as currently amended.

Further, similar to *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988), where the Court of Appeals for the Federal Circuit (hereinafter “the CAFC”) reversed the Patent Office’s determination that the claims at issue did not satisfy the enablement requirement, Applicants respectfully submit that the subject application provides “considerable direction and guidance” in the specification; there was “a high level of skill in the art at the time the application was filed;” and “all of the methods needed to practice the invention were well known.” MPEP § 2164.01(a) (quoting *In re Wands*, 858 F.2d at 740, 8 U.S.P.Q.2d at 1046 and noting that the court concluded that “it would not require undue experimentation . . . to practice the claimed invention”).

It also appears that the Office Action is requiring Applicants to provide working examples of how the claimed compositions can be applied to actual affinity chromatography. Applicants note that “[c]ompliance with the enablement requirement . . . does not turn on whether an example is disclosed.” MPEP § 2164.02. Further, “[a]n applicant need not have actually reduced the invention to practice prior to filing.” *Id.* (discussing *Gould v. Quiqq*, 822 F.2d 1074, 1078, 3 U.S.P.Q.2d 1302, 1304 (Fed. Cir. 1987)). Additionally, “[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *Id.* (citing *In re Borkowski*, 422, F.2d 904, 908, 164, U.S.P.Q. 642, 645 (C.C.P.A. 1970)). Finally, “if all of the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled.” *Id.* (noting that a “lack of working examples . . . should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement”).

More particularly, on Page 4 of the Office Action in reference to the Declaration of Steven E. Hall filed concurrently with the Amendment dated January 27, 2007, the Examiner expresses doubts that one or ordinary skill could reproduce the results provided therein because of the allegedly meager experimental results provided. To address the Examiner’s comments,

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Applicants have enclosed herewith as **Exhibit A** an amended Rule 37 C.F.R. § 1.132 Declaration of Dr. Steven E. Hall, which provides, *inter alia*, additional description of the buffers used and the abbreviations used in the second and third columns of Table A1.

Also on Page 4 of the Office Action, the Examiner asserts that the process steps a)-c) of claim 28 are described only with the generic terms “coupling,” “end-capping,” and “reacting” but without the specific terminology necessary to allegedly adequately define the scope of the particular process steps necessary to produce the products embodied herein.

Applicants respectfully submit that one of ordinary skill in the art upon review of the presently disclosed subject matter could ascertain the scope of process steps a)-c) of claim 28. More particularly, Applicants note that the steps of “coupling,” “end-capping,” and “reacting” are described in the specification as originally filed. For example, the step of “coupling” the linker to the solid support resin is described generally on page 42, lines 21-30, through page 43, lines 5-9. The step of “end-capping” is described generally on page 43, lines 10-15. Further, additional description of “coupling,” “end-capping,” and “reacting,” i.e., reacting a nucleotide with the linker arm attached to the solid support, is provided in the numerous examples. Accordingly, Applicants respectfully submit that the terminology recited in steps a)-c) of claim 28 adequately define the scope of the process steps necessary to produce the products embodied in claim 28.

In sum, Applicants respectfully submit that the specification as originally filed enables one of ordinary skill in the art to make or use the subject matter commensurate in scope with the claims as currently amended without undue experimentation. Accordingly, in view of the above Amendment and Remarks, and the experimental data presented in the Rule 37 C.F.R. § 1.132 Declaration of Dr. Steven E. Hall, Applicants respectfully request that the rejection of claims 1-31 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, be withdrawn at this time. Applicants respectfully submit that claims 9-10, 22-28, and 31 as currently amended are in condition for allowance and respectfully request the same.

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The Objection of Claims 1, 23-28, and 31 Should Be Withdrawn

Claims 1, 23-28, and 31 are objected to because of the following informalities. In claim 1, at line 2, claim 28, at line 2, and claim 31, at line 4, the term “a general formula” allegedly is grammatically incorrect. The Examiner also notes that the same issue arises in claims 23-27, at line 3, in relation to the term “a general structure.” Applicants have canceled claim 1 and have amended claims 28 and 31 by replacing the modifier “a” with “the” in relation to the term “a general formula.” Similar amendments have been made to claims 23-27 in relation to the term “a general structure.”

Applicants respectfully submit that the objections to claims 23-28 and 31 have been addressed. Applicants further submit that claims 23-28 and 31 as currently amended are in condition for allowance and respectfully request the same.

The Rejection of Claims 1-6, 8, 16-28, and 31 Under 35 U.S.C. § 112,

Second Paragraph Should Be Withdrawn

Claim 1-6, 8, 16-28 and 31 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for the following reasons, which are addressed in the order as they are presented in the Office Action.

The Office Action asserts that in claim 1, line 1, and also in claims 2-8 and 16-27, the term “composition” is technically erroneous because the term allegedly implies the presence of two or more separate substances. The Examiner suggests that the term “non-homogeneous solid support” can be substituted for the term “composition” and will not constitute new matter. Accordingly, Applicants have amended claims 22-27 by substituting the term “non-homogeneous solid support” for the term “composition.” Applicants have made similar amendments throughout the Specification. Further, in view of the present Amendments, Applicants have canceled claim 8 and have amended claims 9 and 10 to now depend from new claim 32. The preambles of claims 9 and 10 also have been amended to recite an alkyl-linked nucleotide non-homogeneous solid support to reflect the preamble of new claim 32, from which they now depend.

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On page 5 of the Office Action, the Examiner asserts that in claim 1, lines 4-10, and in claims 28 and 31, the term “substituted” renders the claim incompletely defined. Applicants have canceled claim 1, have added new claim 32, and have amended claims 28 and 31 to include specific structures representative of the group –R₂–K– of Formula I.

The Office Action asserts that in claim 1, at line 12, and claims 28 and 31, the term “phosphate group mimic” allegedly renders the instant claims indefinite because the noted term is not further defined in the claim. Applicants have canceled claim 1 and have amended claims 28 and 31 by defining the variable “P” to be a phosphate or thiophosphate group.

On page 6, the Office Action asserts that in claim 2, at line 1, the term “further comprises” is incorrect. Applicants have canceled claim 2, thereby rendering moot this rejection.

The Office Action also asserts that a similar issue arises in claim 3. Applicants have canceled claim 3, thereby rendering moot this rejection.

The Office Action on Page 6 asserts that in claim 22, and in claims 23-27, the term “adenosine, ... and uridine” are directed to compounds, not substituents and on Page 7, further asserts that the term should read –5-deoxy-5’-adenosinyl– and the like. . Applicants have amended claims 22-27 by amending the terms “adenosine, guanosine, ...” and the like to read “adenosinyl, guanosinyl, ...” and the like and by inserting the term –5-deoxy-5’– where appropriate. Claims 22-27 also have been amended to depend from new claim 32.

The Office Action asserts that the term “analog” in claim 22 is indefinite because there is no further definition of what chemical structures are intended to be included within the scope of the claim. Applicants respectfully submit that one of ordinary skill in the art upon review of the instant disclosure would recognize what is meant by the term “analog.” Applicants note that references describing the isolation or synthesis of nucleoside analogs are incorporated by reference on page 15 of the application as filed. Applicants further note that exemplary, non-limiting examples of γ-alkyl-linked nucleotide analogs of Formulae LII-LV are disclosed on page 33 of the application as filed. Additionally, exemplary ATP analogs are disclosed on pages 37- 39 of the application as filed. Further, non-limiting examples of nucleoside analogs are disclosed on page 40, lines 17-29, of the application as filed.

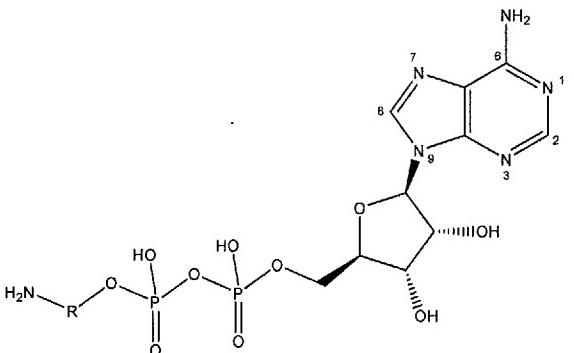
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The Rejection of Claims 1-4, 8-15, and 17-31 Under
35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-4, 8-15, and 17-31 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Trayer et al. in view of Van Aerschot et al and further in view of Shibaev et al. More particularly, the Office Action asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made, based on the teachings of Trayer et al. to make compounds including the linkers of Van Aerschot et al. and the phosphoramidate nucleotide attachment linkage of Shibaev et al. to generate compounds which allegedly would read on the instant claimed subject matter. Further, the Office Action asserts, based on the teachings of Trayer et al., one of ordinary skill in the art would expect that the resultant compounds would be useful in affinity chromatography

Preliminarily, Applicants note that “[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.” MPEP § 2143.03 (citing *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974)). Applicants respectfully submit that neither Trayer et al. and/or Van Aerschot et al. and/or Shibaev et al., either alone or in combination, teach or suggest all of the claim limitations of the pending claims as currently amended.

Applicants note that Trayer et al. discloses a ligand, for example, compound C in Figure 1, having the following formula:



wherein R is $-(CH_2)_6-$. Trayer et al. also discloses ligands wherein an alkylamine linker is attached to either position 8 of the purine ring, e.g., Compound A of Figure 1, or position 6 of the purine ring, e.g., Compound B of Figure 1. Applicants further note that ligands disclosed in

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Trayer et al., having an alkylamine linker attached to, for example, a pyrophosphate group, wherein the linker is attached to the pyrophosphate group through an oxygen atom.

As noted in the Amendment dated January 26, 2007, one of ordinary skill in the art upon review of the presently disclosed subject matter would recognize that the ligands disclosed in Trayer et al. differ from the compositions of the instant claims as presently amended in that the alkylamine linker disclosed in Trayer et al. is attached to the beta-phosphorous atom of an ADP (or gamma-phosphate of an ATP molecule) molecule through an oxygen atom, whereas the linker group of the presently claimed compounds is attached through a nitrogen atom. Thus, Trayer et al., neither alone or in combination with Van Aerschot et al., discloses, teaches, or suggests an alkylamine linker attached to the beta-phosphorous atom of an ADP molecule or a gamma-phosphorous atom of an ATP molecule through a nitrogen atom.

Further, Applicants note that the affinity adsorbent disclosed in Shibaev et al. includes a straight-chain divalent alkyl linker having six carbons. Trayer et al. and Shibaev et al., either alone or in combination, are silent, however, with regard to the loading of the alkyl-linked nucleotide on the solid support. Applicants have added new claim 32 and amended claims 28 and 31 to include embodiments wherein the solid support has a loading of an alkyl-linked nucleotide in a range of 20-50%, i.e., 20-50% of reactive sites on the solid support are reacted with an alkyl-linked nucleotide. Support for this amendment can be found in claim 12 as originally filed, and on page 45, lines 7-14, of the application as originally filed. Applicants respectfully submit that neither Trayer et al., Van Aerschot et al., nor Shibaev et al., either alone or in combination, suggest an alkyl-linked nucleotide non-homogeneous solid support as described in the presently amended claims.

Applicants respectfully submit that the linker loading can influence the performance characteristics of ligands bound to a solid substrate for use, for example, in affinity chromatography, e.g., to profile compound libraries for drug discovery. See, for example, Figure A2, in Appendix A of the amended Rule 37 C.F.R. § 1.132 Declaration of Dr. Steven E. Hall, which demonstrates that the loading density of the ligand can influence the elution and/or separation of protein targets.

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Further, Applicants note that the Advisory Action dated October 11, 2007, and the Interview Summaries dated September 12, 2007, and September 27, 2007, raise a possible rejection of claims 1, 28, 31-33 as presented in the Amendment dated September 11, 2007, over Haystead et al., *Eur. J. Biochem.*, 214, 459-476 (1993) [hereinafter “Haystead et al. (1993)”] and Shibaev et al., CAPLUS Accession Number 86, 121683 (1977). Preliminarily, Applicants note that Shibaev et al., CAPLUS Accession Number 86, 121683 (1977), corresponds to Shibaev et al., *Bioorganicheskaya Khimiya*, 3(1), 120-6 (1977), which is of record and is referenced hereinabove.

Applicants note that Haystead et al. (1993) and Shibaev et al., as noted hereinabove, are each silent with regard to the loading of the alkyl-linked nucleotide on the solid support, whereas new claim 32 and amended claims 28 and 31 include embodiments wherein the solid support has a loading of an alkyl-linked nucleotide in a range of 20-50%. Further, Applicants note that both Haystead et al. (1993) and Shibaev et al. disclose a straight-chain divalent alkyl linker having six carbons. In contrast, new claims 32-33 and amended claims 28 and 31 recite divalent linkers having at least 8 carbon or heteroatoms, and in some embodiments, at least 10 or more carbon or heteroatoms. Also, Haystead et al. (1993) requires a phenyl group attached to the gamma phosphate. Applicants respectfully submit that the linkers as recited in the claims as currently amended are neither taught nor suggested by Haystead et al. (1993) or Shibaev et al. either alone or in combination.

In sum, Applicants respectfully submit that all of the claim limitations of claims 9-10, 22-28, and 31 as currently amended are neither taught nor suggested by Trayer et al. and/or Van Aerschot et al. and/or Shibaev et al. and/or Haystead et al. (1993) either alone or in combination. Accordingly, Applicants respectfully submit that the Office Action has not established a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 8-15, and 17-31 under 35 U.S.C. § 103(a) over Trayer et al. in view of Van Aerschot et al. further in view of Shibaev et al. be withdrawn at this time.

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New Claims 32-33 Are in Condition for Allowance

Applicants have added new claims 32-33 by the present Amendment. New claim 32 is directed to an alkyl-linked nucleotide non-homogeneous solid support consisting essentially of the general formula I, wherein particular R₂ groups are recited. Support for new claim 32 can be found in claims 1 and 19 as originally filed and in the numerous Examples. New claim 33 depends from claim 32 and recites particular embodiments of the variables R₁, R₂, P, and n. Support for new claim 33 can be found in claims 1 and 19 as originally filed and in the numerous Examples, in particular Example 45. No new matter has been added. Applicants respectfully submit that new claims 32-33 are in condition for allowance and respectfully request the same.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. § 112, first paragraph; § 112, second paragraph, and § 103(a) are now overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

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Respectfully submitted,

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ELECTRONICALLY FILED USING THE EFS-WEB ELECTRONIC FILING SYSTEM OF THE UNITED STATES PATENT & TRADEMARK OFFICE ON October 11, 2007.